



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup>:</b> <b>A61K 31/52, 31/195, 35/12, 38/43</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/02165</b> <b>(43) International Publication Date:</b> 22 January 1998 (22.01.98)
<b>(21) International Application Number:</b> PCT/US97/12408 <b>(22) International Filing Date:</b> 16 July 1997 (16.07.97)  <b>(30) Priority Data:</b> 08/683,535                      17 July 1996 (17.07.96)                      US  <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US    08/683,535 (CIP) Filed on                                      17 July 1996 (17.07.96)  <b>(71) Applicant (for all designated States except US):</b> NICADA, INC. [US/US]; Suite 209, 2934 1/2 Beverly Glenn Circle, Los Angeles, CA 90077 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SHELL, William, E. [US/US]; 3048 Nicada Drive, Los Angeles, CA 90077 (US). JARMEL, Mark, E. [US/US]; 2808 Angelo Drive, Los Angeles, CA 90077 (US).  <b>(74) Agent:</b> HORTON, Corwin, R.; Suite 2001, The Park, 25 Mann Drive, Kentfield, CA 94904 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> APPETITE SUPPRESSION  <b>(57) Abstract</b> <p>A method and composition for reducing appetite and carbohydrate craving using precursors for the neurotransmitters serotonin, dopamine, norepinephrine and histamine, which include the precursors tryptophan, phenylalanine, tyrosine and histidine. The precursors are combined together and with xanthines for synergistic effect permitting advantageously lower doses of the precursors. Concomitant administration of histidine with any of tryptophan, phenylalanine and tyrosine produces a potentiated effect in appetite suppression. Xanthines, including theobromine, caffeine and cocoa, act as potentiators of the precursors, individually and in combinations of precursors. Separate formulations with xanthines of tyrosine and/or phenylalanine are used conjointly with a formulation of tryptophan with xanthines, each administered separately at intervals of at least 20 minutes. Hydrolyzed protein is utilized as a natural tryptophan source for the combinations, together with an insulin producing carbohydrate to remove from the blood stream other amino acids competing for transport across the blood-brain barrier. Alternatively, unhydrolyzed protein may be administered along with a proteolytic enzyme to produce tryptophan in the gastrointestinal tract.</p>		

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## Description

### APPETITE SUPPRESSION

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#### Technical Field

10 This invention relates generally to dietary supplements for reducing appetite and decreasing carbohydrate craving. There has been increasing attention to weight control since obesity is associated with an increased mortality rate, diabetes mellitus, hypertension, heart disease and stroke. The attention to reducing obesity has lead to the introduction of sugar-free and fat-free foods, diet plans, weight  
15 reduction programs, artificial fats, and pharmaceutical agents to alter both appetite and carbohydrate craving. Despite the desirability of reducing weight and the proliferation of products to aide in weight reduction, the weight of the population continues to rise. It is now estimated that more than 40% of the population is significantly  
20 overweight. At any given time approximately 25% of the population is on a diet, leading to undesirable "yo-yo" effects from repeated dieting. The failure of weight reduction products to achieve and to sustain weight loss can be attributed to several factors. These include the relative ineffectiveness of the individual approaches, side effects of  
25 weight loss products, and the cost of a sustained weight loss program. Accordingly, there is a need for an effective program based on safe naturally occurring agents. Such a program will allow weight loss with reduced side effects and reduction of costs.

#### 30 Background Art

One major component of a successful weight loss program is appetite suppression. Appetite suppression has been achieved with administration of amphetamines, antidepressants, both soluble and  
35 insoluble fibers, serotonin precursors, and prescription drugs which enhance serotonin activity. All of these techniques, as currently applied, have significant disadvantages.

Amphetamines are well known to reduce appetite. Dexedrine and related agents including ephedrine and pseudoephedrine reduce appetite. These agents either produce agitation, addiction or nerve damage (dexedrine), or produce rapid attenuation of effect (ephedrine or pseudoephedrine). Phentermine, an amphetamine-like molecule, is approved for use as an appetite suppressant, but must be administered by prescription. This results in increased costs associated with physician visits. Additionally, phentermine can only be used for short periods when administered by itself. It is believed that the amphetamines, including phentermine, suppress appetite in part through their effects on brain dopamine. Phentermine also can cause hypertension, heart irregularities and agitation. Thus, the amphetamines and related agents can be used for appetite reduction, but at substantial cost and with known, often unacceptable side effects.

One approach, introduced by Wurtman and associates in 1978, was to use precursors of brain serotonin to reduce appetite for carbohydrate. Serotonin within the hypothalamic region of the brain is known to reduce craving for carbohydrates. In Wurtman, et al U.S. Patent No. 4,210,637, a composition and method for selectively suppressing appetite for carbohydrates is described. This method includes the administration of the serotonin precursor, tryptophan, along with a carbohydrate that causes insulin secretion. Secretion of insulin moves amino acids other than tryptophan from the bloodstream into the tissues. This removes amino acids from the blood which compete with tryptophan for transport across the blood-brain barrier. This carbohydrate-initiated insulin effect on circulating amino acids maximizes delivery of tryptophan to the hypothalamus.

The dose of tryptophan proposed by Wurtman is between 10 and 100 mg per kg. in rats. For a 70 kg man, the dose would range between 700 and 7,000 mg to potentially achieve similar effects. When Wurtman applied tryptophan administration to humans in an amount of 2,300 mg per day, there was no consistent effect on appetite suppression. Moreover, the regulatory agency in the United States, the Food and Drug Administration (FDA), has found that tryptophan in doses of more than 100 mg per day may be unsafe. The FDA has determined that doses of tryptophan in excess of 100 mg per day may

potentially cause muscle damage. Accordingly, tryptophan is not being used alone, or administered with a carbohydrate, as an appetite aide.

Wurtman, et al in U.S. Patent No. 4,309,445 described a composition and method using d-fenfluramine to block intermittent carbohydrate cravings. This method disclosed that d-fenfluramine and the related isomer l-fenfluramine selectively reduces carbohydrate craving. Wurtman, et al, in U.S. Patent 4,687,763 disclosed that tryptophan can increase brain serotonin levels when given with melatonin. In this patent Wurtman, et al, disclosed that oral administration of tryptophan can increase brain serotonin and that increased brain serotonin leads to reduced carbohydrate craving. The amount of tryptophan used by Wurtman, et al, were consistently been between 2 and 100 mg/kg. of body weight per dose. These amounts are significantly above the current FDA safety guidelines of less than 1.6 mg/kg per day of supplemental tryptophan, particularly if the tryptophan comes from bacterial synthesized sources.

The FDA only allows naturally occurring protein to be used as a source of supplemental tryptophan. Both intact and "predigested" (enzyme hydrolyzed), forms of naturally occurring protein may be used. Naturally occurring protein contains approximately 1.6 % tryptophan. The amount of tryptophan in naturally occurring protein has previously been considered insufficient to produce a reduction in carbohydrate craving. This is due to the presence of other amino acids which compete for absorption with the small amount of tryptophan present in protein. In a recent FDA publication, it was concluded that there was insufficient evidence that tryptophan reduces appetite in doses considered safe. There is no known prior art suggesting the use of predigested protein as a source of tryptophan for appetite suppression.

Tyrosine is a precursor of brain dopamine. Amphetamines stimulate the release of dopamine. Brain dopamine is associated with the appetite suppressing effects of amphetamine-like agents. To date, a food supplement has not been used to enhance the release of dopamine without using amphetamines or amphetamine-like agents such as ephedrine or pseudoephedrine. Wurtman, et al, in U.S. Patent No. 4,673,689 disclose that tyrosine can be used to potentiate the sympathomimetic agents such as ephedrine or pseudoephedrine. However, this patent contains no disclosure or suggestion of any

usefulness or synergism for any purpose for combining tyrosine with any other agents active in the central nervous system.

Histidine is a precursor of histamine in the brain. It has been reported that histamine and its precursor histidine will decrease the food intake of experimental animals (rats) when administered by intraperitoneal injection ("Manipulation of Central Nervous System Histamine, Histaminergic Receptors (H1) Affects Food Intake in Rats," Mercer et al., J. of Nutrition, 1994, Vol. 24, pp 1029-1036) ) However, the effectiveness of either histamine or its precursor histidine for suppression of appetite by oral administration or at dosage levels at which the known side effects could be tolerated has not been elucidated.

Chocolate, particularly the cocoa powder, contains among other active ingredients, the xanthines theobromine and caffeine; as well as biogenic amines such as phenylethylamine. These agents influence the activity of both serotonin and dopamine. Xanthines are known to increase the release of both dopamine and serotonin. Neither chocolate or cocoa powder have been used as appetite suppressants either alone or in combination with neurotransmitter precursors such as tryptophan or tyrosine. Phenylethylamines are also known to stimulate the release of serotonin and dopamine. Phenylethylamines are also known to act as inhibitors of the enzyme monoamine oxidase (MAO), which breaks down serotonin and dopamine. Chocolate has been used both directly and indirectly, knowingly and unknowingly, as a mood elevator. The mechanism of chocolate's appeal has, heretofore, not been specifically defined. Most common knowledge attributes the appeal of chocolate to its taste, not to neurotransmitter affects.

In 1992, Wientraub observed that phentermine and fenfluramine when used together induced long term weight loss, reduced appetite and reduced carbohydrate craving. Fenfluramine is the mixture of the dextro and levo forms of fenfluramine. The results of using phentermine and fenfluramine in combination was attributed to their separate effects on serotonin and dopamine. Using this combination of prescription drugs, weight loss could be sustained for months to years. Accordingly, there has been a substantial increase in the use of the phentermine-fenfluramine approach to weight loss despite the lack of regulatory approval of the the combination. Many regulatory agencies limit the use of either agent to short periods ranging from 7 days to 1

month. In addition, the use of fenfluramine has been associated with the side effect of pulmonary hypertension and heart valve disease in rare instances. The use of d-fenfluramine induces grogginess in many subjects and is expensive, often costing US\$5.00 per day for the drug.

- 5 This cost is in addition to multiple visits to physicians for monitoring of treatment which may last many months or years. Also, phentermine is an amphetamine-like drug whose long term effects are unknown. Accordingly, there is a need for a low cost program that emulates the effects of the phentermine-fenfluramine therapies that can be applied to
- 10 a large number of individuals without repetitive physician monitoring. Ideally, the components of such a program would be formulated from low cost ingredients which are not drug.

#### Disclosure of the Invention

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- This invention has the object of achieving appetite suppression and reduced carbohydrate craving without large doses of fibers, amphetamines, antidepressants, or other prescription drugs. This invention also has the object of enabling use of readily available, low
- 20 cost, safe, plant-derived agents and to provide appetite suppression with such agents at reduced dosage to minimize the possibility of side effects.

- This invention provides methods and compositions for suppressing appetite based upon the discovery that certain neurotransmitter precursors will act synergistically with each other and
- 25 with certain neurotransmitter potentiators in suppressing appetite and reducing carbohydrate craving. In particular, neurotransmitter precursors for the neurotransmitters serotonin, dopamine, norepinephrine and histamine, which contain an amine group and include tryptophan, phenylalanine, tyrosine and histidine, are orally
- 30 administered in reduced doses concomitantly with one or more xanthines, and particularly caffeine and/or theobromine effectively to suppress appetite. When administered alone, these neurotransmitter precursors require unacceptably high doses in order to suppress appetite.

- In a further aspect of this invention histidine is administered
- 35 concomitantly with either tryptophan, phenylalanine or tyrosine with synergistic effect to suppress appetite, either with or without the concomitant administration of a xanthine. Tryptophan may be

administered conjointly with phenylalanine or tyrosine with beneficial effect, during the same day but with administration of one separated by at least 20 minutes of the other, to avoid competition between them for entry across the blood-brain barrier.

5 In another feature of the invention the neurotransmitter precursor and potentiators are administered in accordance with this invention in naturally occurring forms long considered safe for ingestion as a food stuff. The neurotransmitter precursor tryptophan may be administered in the form of natural proteins which have been  
10 hydrolyzed to release amino acid residues including tryptophan. The predigested protein allows delivery of free amino acids so that a rapid effect can be produced. The hydrolyzed protein is advantageously administered concomitantly with a carbohydrate to a subject having an empty stomach (i.e. at least an hour after eating) to trigger insulin  
15 secretion to clear from the bloodstream competing amino acids that would otherwise block passage of tryptophan across the blood-brain barrier, thereby maximizing the absorption of naturally occurring tryptophan. This insulin-mediated effect on amino acids allows sufficient tryptophan to be delivered to the brain so that the desired  
20 effects are achieved.

In a related embodiment, rather than administering prehydrolyzed protein, the protein source for the tryptophan may be administered in unhydrolyzed form, together with a proteolytic enzyme, so that hydrolysis occurs in the gastrointestinal tract to release  
25 the tryptophan.

Xanthines are also advantageously derived from natural sources long employed in foodstuffs, such as cocoa, tea, coffee and the like. Cocoa in particular provides a unique source of a combination of both the xanthines caffeine and theobromine and phenylethylamine that is  
30 quite palatable and considered safe.

Dosage forms are provided to advantageously and conveniently carry out the foregoing methods with reduced dosages consistent with effective suppression of appetite. The single dosage forms constitute, pills, capulets and other forms individualized for administering the  
35 appropriate single dose quantities of the selected constituents. The amount of tryptophan in the dosage forms is from about 2.5 to 100 milligrams, the amount of tyrosine is from about 10 to 700 milligrams,



the amount of histidine from about 1 to 500 milligrams. Where they present in the dosage forms, the xanthine theobromine is in the range of from about 1 mg. to 2 gm. or higher. Where cocoa is employed as the xanthine source, it may be present in the single dosage form in the amount of about 1 mg. to 2 grams or higher. Where, hydrolyzed protein is the source of tryptophan, the amount of hydrolyzed protein may be between one half of a gram. and 30 grams or higher. Desirably, the amount of hydrolyzed protein is selected to provide therein an amount of tryptophan of between 2.5 to 100 milligrams.

These combinations of agents, due to their surprising synergism, allows the dose of the individual neurotransmitter precursors to be reduced, thus reduce side effects and to reduce component doses to levels generally considered safe by regulatory agencies, such as the FDA. They additionally enable the use of naturally occurring protein and plant-derived substances instead of drugs.

Under FDA regulations supplemental tryptophan cannot be synthesized by man-made processes and thus they must be derived from naturally occurring protein, either animal or vegetable. The FDA further stipulates that the dose of added tryptophan cannot exceed 100 mg per day, or 1.43 mg/kg per day. The preferred source for our invention is vegetable protein and a dose of tryptophan is 45 mg/dose or 0.71 mg/kg per day. The amount of tryptophan in the embodiment using predigested protein can be as low as 15 to 40 mg per dose. These doses of tryptophan, which comply with the FDA limitations, would be ineffective in the absence of the xanthines

### Best Mode of Carrying Out The Invention

The following description illustrates the manner in which the principles of the invention are applied but is not to be construed as limiting the scope of the invention.

Serotonin, dopamine, norepinephrine and histamine form a class of neurotransmitters that are active in the CNS to affect appetite, either stimulating the release of corticotropin-releasing factor (CRF), which suppresses appetite, or suppressing the release and/or activity of neuropeptide Y, which stimulates appetite. Serotonin, norepinephrine

and histamine all stimulate the release of CRF. Dopamine suppresses neuropeptide Y. Histamine additionally promotes neuron firing.

5 The precursors for this class of neurotransmitters, all of which contain an amine group, include tryptophan for serotonin, phenylalanine and tyrosine for both dopamine and norepinephrine and histidine for histamine. In this invention, these precursors are employed in combination with each other and in combination with xanthines to potentiate the effect on appetite suppression by the respective neurotransmitters of this class.

10 The precursors are employed in this invention to enhance the synthesis of their respective neurotransmitters and since serotonin, phenylalanine, tyrosine and histidine all enhance synthesis of neurotransmitters that stimulate release of CRF, these precursors all thereby indirectly stimulate release of CRF. Additionally, phenylalanine  
15 and tyrosine indirectly suppresses neuropeptide Y through enhancement of the synthesis of dopamine as well. Also, histidine promotes neuron firing thereby indirectly stimulating synthesis of norepinephrine, tyrosine and serotonin.

The precursors may be employed in this invention in pure form,  
20 e.g. exogenous material synthesized or derived from animal or vegetable protein, particularly purified extracts isolated from the amino acid residues in enzyme hydrolyzed proteins. However, a source for the precursor tryptophan particularly useful in this invention, both because it is a natural food source and because of the regulatory restrictions, are  
25 proteins, either enzyme hydrolyzed prior to administration to release tryptophan or unhydrolyzed protein to be administered along with a proteolytic enzyme that will liberate the tryptophan in the gastrointestinal tract. Commercial preparations of predigested proteins, typically from milk-derived protein, such as casein or whey, are  
30 available and may be administered separately or in composition with histidine and/or a xanthine.

Where the tryptophan is to be administered in the form of a predigested protein or a protein to be enzyme hydrolyzed upon administration, it is important in this invention to administer the  
35 protein concomitantly with a carbohydrate, and particularly sugar, dextrins, starch and the like, in order to cause release of insulin to

remove from the blood stream the other amino acids competing with tryptophan for transport across the blood-brain barrier.

Where unhydrolyzed protein is administered together with a proteolytic enzyme, soluble proteins, such as albumin, are preferred, for ease of breakdown. Whey, casein and soy are convenient protein sources. Proteolytic enzymes may include papain, chymopapain, bromelin, trypsin and pepsin.

Xanthines constitute a class of non-selective adenosine antagonists and they include theobromine, caffeine and theophylline. They are capable of promoting release of the neurotransmitters serotonin, dopamine and histamine. and they potentiate neurotransmitter synthesis for each when administered in accordance with this invention. Combining xanthines, and neurotransmitter precursors allows the desired effects to be achieved with reduced, safe, doses of neurotransmitter precursors.

The xanthines may be used in the form of their free compounds or as their salts, adducts or other derivatives, for example citrated caffeine, theophylline ethylenediamine, theophylline sodium acetate, sodium glycinate, the choline salt, the theophylline derivatives theophylline-megumine and dyphylline, theobromine calcium salicylate, sodium acetate or sodium salicylate.

A particularly suitable source of xanthines for use in this invention are those from natural sources. Cocoa provides a unique combination of xanthines, including theobromine and caffeine, and biogenic amines, and particularly phenylethylamine, in a form that is normally easily ingested and tolerated by the subject. In addition to the potentiating effect of the xanthines in cocoa, the MAO-inhibiting action of the phenylethylamine prolong the effects of serotonin, histamine and/or dopamine. Cocoa powder was originally included in preliminary formulations with neurotransmitter precursors to improve flavor and because its mood enhancing effects have appealed to people for centuries. An unexpected result was that the cocoa powder significantly potentiated the effects of the neurotransmitter precursors. This potentiating effect was determined by us to be produced by the naturally occurring xanthines and biogenic amines present in cocoa powder.

Infusions of caffeine from coffee beans and of caffeine and theophylline from tea leaves may be employed as a natural source of these xanthines, either in liquid form as coffee and tea, or in dried extract form, alone or, more inconveniently, in composition with the neurotransmitter precursor. Chocolate, guarana and other food sources may be employed.

The combinations of neurotransmitter precursors of this invention may be employed with an attendant synergistic effect, without concomitant administration of xanthine, and yet further potentiation may be achieved by administering the neurotransmitter precursor combinations with a xanthine. The neurotransmitter precursor combinations include histidine administered with tyrosine or with tryptophan and tyrosine followed by tryptophan after a time delay. Histidine does not compete with either tyrosine or tryptophan in crossing the blood-brain barrier so may be administered with either tyrosine or tryptophan at the same time and in the same composition.

Tyrosine and phenylalanine may be used conjointly with tryptophan in this invention with advantage but as they can inhibit passage of tryptophan across the blood-brain barrier, they are administered to the subject separately from the tryptophan, at time intervals of at least twenty minutes. Either the tryptophan or the tyrosine and/or phenylalanine may be administered before the other. Administered in this fashion to first permit take up of the phenylalanine and/or tyrosine from the blood stream, inhibition of tryptophan take-up is avoided and enhanced effect of the precursors is attained. Additionally, neurotransmitter balance is fostered by decreasing the total dose over time of any single neurotransmitter.

While it is not intended to be bound by any theory, the unexpected synergism found between these precursors may be at least partially explained by the different mechanisms mediated by their respective neurotransmitters in stimulating release of CRF and/or suppressing neuropeptide Y.

The dosage of each neurotransmitter precursor is in an amount sufficient to enhance synthesis of its respective neurotransmitter(s), to stimulate the release of CRF and thereby to suppress appetite in combined administration with the other neurotransmitter and or xanthines employed. The synergistic effect of these combinations will

permit appetite suppression at lower dosage levels of each of the neurotransmitter precursors than otherwise possible and desirably these lower dosage levels are employed to avoid possible side effects and particularly those now limiting the use of at tryptophan, including  
5 grogginess.

For tryptophan the desired single dose range is between 2.5 and 100 mg. with a typical dose of 45 mg. The desired dosage range of either phenylalanine or tyrosine is between 10 and 600 mg., with a typical dose of 500 mg. However, doses up to 700 mg. or even to 1 gram or higher,  
10 e.g. up to 3 grams, may be administered without undue risk of side effects. These amounts, equivalent to from .14 to 42.2 mg/kg, would be insufficient to suppress appetite if used alone. Histidine is desirably administered in a dosage range of 1 to 500 mg., with a typical dose of 30 mg. However somewhat higher doses, e.g. up to 1 gram, may be given,  
15 if tolerated by the subject. The dosage range for each precursor applies to combined administration of the precursor with another precursor, with a xanthine, or with both.

Where hydrolyzed proteins or proteins to be hydrolyzed in the gastrointestinal tract are employed as the source of tryptophan, the  
20 proteins should be in an amount to provide the tryptophan dosage levels of this invention as discussed above. Typically, this will be in a range of between around one half of a gram and 30 gm. The amount of enzyme employed may be 30 to 50 mg. per gram of protein. Insulin producing carbohydrates administered with the protein are desirably at  
25 dosage levels of from about one half gram to 5 grams.

Xanthines are employed in this invention in dosage ranges appropriate to promote release of neurotransmitters and to avoid undesired side effects. Theobromine and theophylline may each be administered in a dosage of from 1 mg. to 2 grams or higher. Caffeine  
30 may be administered in a dose of from 1 to 200 mg. or higher, if tolerated by the subject. Cocoa may be administered in a dose of 1 mg. to 2 grams or higher up to 20 grams for an appropriate dose of xanthines, with a preferred dose being 400 to 800 mg. Infusions such as tea or coffee may be employed, with one to two cups providing an appropriate dose.  
35 Somewhat higher doses of these xanthines may be employed with some subjects without undue discomfort.

The neurotransmitter precursors and neurotransmitter potentiators of this invention may be administered orally separately, or, for assurance of appropriate proportions and dosages as well as for convenience, they are administered together in the same composition.

5 The dosage forms for administration separately or in the same composition may be any of the conventional forms, including capsules, capulets, chewable wafers, tablets, liquid suspensions, powders and the like. Xanthine dosages may take the form of chocolate preparations, cocoa drinks, infusions, e.g. coffee and tea and cola drinks containing  
10 caffeine. Hydrolyzed protein sources of tryptophan may be taken separately in tablet form, utilizing commercially available predigested protein tablets, such as LLP Concentrated Predigested Protein sold by Twin Laboratories, Inc., Ronkonkoma, New York containing  
15 approximately 18 mg. of tryptophan per 1 gram tablet.

The compositions in the form of powders or liquids may be packaged in multiple dosage quantities with instructions to the user to extract therefrom for ingestion appropriate individual dosage amounts, e.g. a teaspoonful. However, the compositions are desirably prepared in discrete units, e.g. capsules, wafers etc., which each contain the  
20 appropriate dosage amounts of neurotransmitter precursors and/or neurotransmitter potentiators for a single dose as discussed above.

The compositions may include the usual carriers, fillers, excipients and adjuvants. Advantageously, they include soluble fiber, insoluble fiber, neurotransmitter precursors and the potentiating agents  
25 contained in cocoa powder. The inclusion of dietary fibers produces early satiety from volume distention and causes further appetite suppression by triggering the release of CCK. The appetite suppressing actions of the dietary fiber component further enhance the invention's neurotransmitter-related effects. They additionally may contain folic  
30 acid and vitamin B6 to enhance conversion of tryptophan to serotonin, tyrosine to dopamine and histidine to histamine, respectively.

The preferred amount of folic acid is 200 mcg per dose with a range of 1 - 800 mcg/dose. The preferred amount of vitamin B6 is 10 mg with a range of 1 - 50 mg/dose. Representative doses of soluble fibers are  
35 100 mg to 1000 mg per dose. The best soluble fibers for producing appetite suppression are pectin fibers from apple or citrus. fruits. Representative doses of insoluble fibers are 100 mg to 1000 mg per dose.

A preferred embodiment utilizes insoluble fiber in the form of wheat bran for these formulations. Other suitable insoluble fibers include, but are not limited to cellulose, methyl-cellulose, chitosan, whey, whole wheat fiber, and other whole grain fiber. These concentration of insoluble fibers would be ineffective as appetite suppressants if given alone in these doses. The fibers must be premixed with water until barely wet and dried at low heat. The premix will result in a better gel and fat binding than the use of either type of fiber alone. Fiber which has not been premixed and heated to dryness will reduce the effectiveness of the formulations.

It is important in carrying out the invention to administer the dosages when the subject has an empty stomach, typically at least an hour after the subject has eaten in order to avoid undesirably slow uptake across the blood-brain barrier, due to competition with other amino acids from the ingested food. Administration may be repeated as desired, at intervals throughout the day.

The effects of the formations of this invention normally should be sufficiently potent that their effects can be experienced after the first dose. Their effectiveness can be detected by a given individual using a questionnaire to assess hunger and carbohydrate craving. This is in contradistinction to other appetite suppressants that require multiple doses or indirect methods such as weight loss to assess their effectiveness.

The various embodiments of the invention utilizing tryptophan, phenylalanine or tyrosine as the sole neurotransmitter precursor or combined with histidine, may be used alone. Advantageously, however, these tryptophan and phenylalanine or tyrosine formulations are given to a subject, but at different times, each to produce appetite suppression, but by different modalities. The phenylalanine or tyrosine-containing formulations are designed to potentiate the production and release of dopamine. Appetite suppression is achieved by the resulting activity of dopamine, and of histamine, if histidine is included. The phenylalanine or tyrosine-containing formulations emulate the effects of amphetamines, phentermine, ephedrine and pseudoephedrine. Tryptophan-containing formulations are designed to reduce appetite for 2-4 hours and are designed to potentiate the production and release of serotonin, and of histamine, if histidine is

included. Appetite suppression and reduced carbohydrate craving is achieved by the resulting activity of serotonin. The tryptophan-containing formulations emulate the effects of fenfluramine, d-fenfluramine and fluoxetine and are typically designed to reduce appetite for 1-4 hours and to reduce carbohydrate craving for 16-36 hours.

The tryptophan and phenylalanine or tyrosine formulations may be designed for use together in varying dosage schedules depending on individual needs. It is preferred that each to be taken on an empty stomach. When used together in accordance with this invention, typically during the same day (24 hours), one is administered separately at least 20 minutes after the other. This is done to avoid competition of the precursors for entry across the blood brain barrier. Typically, the phenylalanine or tyrosine formulation is given before lunch to suppress appetite during the day and afternoon. The tryptophan formulation is given before dinner to decrease appetite and reduce carbohydrate craving at dinner and during the evening. Late afternoon and evening hours are the times of day when many over-weight people crave both food and carbohydrates. Alternately, The phenylalanine or tyrosine formulation can be administered at 10:00 a.m. and at 3:00 p.m. with the tryptophan formulation being administered at 11:00 a.m. and 4:00 p.m.. The dosage schedule allows these food supplements to emulate the effects of the prescription drugs phentermine, fenfluramine, and d-fenfluramine.

If an individual undergoes a fast to induce hunger, administration of tyrosine results in appetite suppression which begins 15 to 30 minutes after ingestion and continues for 2-4 hours. If hunger reappears, re-ingestion of the formulation results in suppression of hunger beginning 15-30 minutes after ingestion and continuing for 2-4 hours. Repeated administration of the tyrosine formulation results in repetitive suppression of appetite.

Administration of the tryptophan-containing formulation after a self-induced fast results in appetite suppression which begins 20-40 minutes after ingestion and continues for 2-4 hours. A reduction of carbohydrate craving begins approximately 30 minutes after ingestion of the tryptophan formulation and continues for 18-36 hours. If the tryptophan formulation is administered 30-90 minutes before the



tryptophan, the onset of the tryptophan formulation effects is reduced to 15-30 minutes.

Following Examples 1 through 7 illustrate formulations with tyrosine as the sole neurotransmitter precursor and formulations with tryptophan as the sole neurotransmitter precursor and use thereof independently and together. These examples also illustrate the use of various xanthines with the precursors and the use of hydrolyzed protein as the source of tryptophan.

10

### Example 1

A useful tyrosine formulation in one dose is tyrosine 295 mg, soluble fiber 125 mg, insoluble fiber 125 mg, cocoa 200 mg, vitamin B6 5 mg, and folic acid 100 mcg. A useful tryptophan combination per dose is soluble fiber 175 mg, insoluble fiber 175 mg, protein powder 100 mg, tryptophan 45 mg, vitamin B6 5 mg, and folic acid 100 mcg. Another useful tryptophan-containing formulation per dose is soluble fiber 175 mg, insoluble fiber 175 mg, predigested protein powder 2,000 mg, cocoa 250 mg, sugar 250 mg, vitamin B6 5 mg, and folic acid 100 mcg.. A preferred dosage of the combination is 2 capsules of tyrosine formulation before lunch, 2 capsules of the tyrosine formulation at 4:00 p.m., and 2 capsules of either of the tryptophan formulations 30 minutes before dinner. Another dosage schedule includes the tyrosine dose at 10:00 a.m. and 3:00 p.m. with tryptophan dose at 11:00 a.m. and 4:00 p.m. Other dosage schedules can be used.

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### Example 2

This example illustrates the use of tyrosine as the sole neurotransmitter precursor, together with xanthines, for appetite suppression. A 53 year old male underwent a 10 hour fast to induce hunger. Two capsules of a tyrosine formulation were given each capsule containing soluble fiber in the form of apple pectin 175 mg, insoluble fiber in the form of bran fiber, tyrosine 295 mg, cocoa powder 200 mg, folic acid 100 mcg and vitamin B6 5 mg. The soluble and insoluble fibers had been premixed, wet and dried. The material had

been placed into capsules. The subject experienced an elimination of hunger that began 8 minutes after ingestion and lasted for 2.5 hours. A second ingestion of 2 capsules of the formulation reproduced the effect.

5

### Example 3

This example illustrate the use of tryptophan as the sole neurotransmitter precursor, together with xanthines, for appetite suppression and carbohydrate craving. A 44 year old male underwent a 10 hour fast to induce hunger. He then ingested 2 capsules of a tryptophan formulation each capsule containing 175 mg soluble fiber in the form of apple pectin and psyllium, 175 mg insoluble fiber in the form of bran fiber, 100 mg vegetable non-soy protein, 45 mg of tryptophan, 250 mg of cocoa powder, 5 mg of vitamin B6, and 100 mcg of folic acid. The individual's hunger began to dissipate in 30 minutes and was completely dissipated in 60 minutes. The ingestion of the formulation resulted in early satiety in the following meal. There was an abolition of carbohydrate craving which lasted for 24 hours. The onset of the appetite suppression following ingestion of the formulation was associated with mental grogginess that lasted for approximately 15 minutes.

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### Example 4

This example illustrates the use of a tryptophan formulation utilizing predigested proteins as the tryptophan source. A 35 year old female underwent a 10 hour fast in order to induce hunger. She then ingested two capsules containing 175 mg soluble fiber in the form of apple pectin and psyllium, 175 mg insoluble fiber in the form of bran fiber, 2,000 mg of predigested protein in the form of predigested casein, 250 mg of cocoa powder, 250 mg sugar, 5 mg of vitamin B6, and 100 mcg of folic acid. She experienced a reduction of appetite and abolition of carbohydrate craving. There was no mental grogginess induced by this formulation.

### Example 5

5 This example illustrates the use tyrosine and tryptophan of this invention together for appetite suppression, decreased carbohydrate craving and weight loss. The 53 year old male took 2 capsules of the formulation of daily at 10:00 am, 2 capsules of the formulation of Example 2 at 4:00 p.m. and 2 capsules of the formulation of Example 3 at 5:00 p.m.. This regimen was continued for 10 days. During the 10 day period, both of the formulations reduced appetite for 2-4 hours after each ingestion. Carbohydrate craving was reduced for 24 hours after ingestion of the tryptophan formulation. By the third day there appeared to be an enhanced effect in that the duration of action of the combined doses were prolonged. By the fifth day there was complete suppression of carbohydrate craving that lasted throughout the 10 day period. There were no observed side effect except for the 15 minutes of grogginess induced by the tryptophan formulation on days 1 and 2. For the first 2 days, the onset of the appetite suppression following ingestion of the tryptophan formulation was associated with mental grogginess that lasted for approximately 15 minutes. By the third day the grogginess effect was lost. The subject initially weighed 159 pounds and by the 10th day, his weight was reduced to 150 pounds.

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### Example 6

This example illustrates the use of tyrosine and tryptophan formulations of the invention together in an open label study of 5 subjects including 3 males and 2 females. Each subject took the tyrosine capsule of Example 2 at 10 AM and a typtophan capsule of Example 3 at 3:30 PM. All 5 subjects reported a decrease in hunger after either dose. All 5 Patients experienced a reduction of carbohydrate craving after the tryptophan capsule.

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### Example 7

This example illustrates the use of tyrosine and tryptophan formulations in a randomized double blind placebo controlled trial in 30 subjects. All 30 subjects underwent a 10 hour fast following which they completed a questionnaire to assess hunger on a 5 point scale and carbohydrate craving also measured on a 5 point scale. The subjects then ingested 2 of the capsules of Example 2 or placebo capsules at 10:00 a.m., followed by a questionnaire at 11:00 a.m.. The subjects again took the Example 2 capsule or placebo at 4:00 p.m. and the Example 3 capsule or placebo at 5:00 p.m. They completed questionnaires at 4:00, 5:00, 6:00 p.m. and at 10:00 a.m. the next morning. In the 15 placebo subjects, ingestion of the placebo was followed by an increase in the hunger index from 2.2 to 2.9 after the first dose of tyrosine,  $p < 0.03$ . In the 15 subjects randomized to receive tyrosine, the hunger index fell from 3.1 to 2.4,  $p < 0.03$ . Comparison of the active to placebo group showed a reduction of the hunger index with a high degree of significance,  $p < 0.01$ . The carbohydrate craving index was also significantly reduced by the tryptophan dose,  $p < 0.01$ . In the active group, 85% of the subjects either reduced their feeling of hunger or cravings for carbohydrate while only 45% of the placebo group experienced either a reduction of hunger or cravings for carbohydrate,  $p < 0.03$ .

Following examples 8 and 9 illustrate the formulation and use of histidine with xanthines, with histidine as the only neurotransmitter precursor.

#### Example 8

A formulation of histidine and cocoa may be prepared by blending these two ingredients in powder form in a proportion of 3 parts histidine and 50 parts cocoa by weight. This product is then portioned into gelatin capsules so that each contains 30 mg. of histidine and 500 mg. cocoa. A one capsule dose of this formulation is best administered on an empty stomach, at least one or two hours after eating. Alternatively, the blended powder may be prepared in the form

of a chewable wafer sized to contain the same dose, by combining with the powder wheat bran, apple pectin and a sweetener.

5

### Example 9

A formulation of histidine and caffeine may be prepared in the same manner as described in example 8 by blending in powder form histidine and caffeine in a proportion of 3 parts histidine and 10 parts caffeine by weight. Single dose capsules are then filled with this blend in an amount to each contain 30 mg. histidine and 100 mg. caffeine. This formulation is administered as in example 8.

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Following examples 10 through 15 illustrate practice of the invention utilizing the combination of histidine with tyrosine and of histidine with tryptophan as neurotransmitter precursors, both with and without concomitant application of xanthines.

20

### Example 10

A formulation of tryptophan and histidine may be prepared by blending these two ingredients in powder form in a proportion of 5 parts tryptophan and 3 parts histidine. This product is then portioned into gelatin capsules so that each contains 50 mg. of tryptophan 30 mg. histidine and the capsules are administered as in Example 8.

30

### Example 11

A formulation as in Example 10 that contains caffeine in addition to tryptophan and histidine may prepared by blending in powder form 10 parts of caffeine with 5 parts tryptophan and 3 parts histidine. Gelatin capsules are filled with the powder blend so that each gelatin capsule contain 50 mg. of tryptophan 30 mg. histidine and 100 mg. of caffeine. This formulation is administered as in example 8.

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### Example 12

5       A formulation of tyrosine and histidine may be prepared by  
blending these two ingredients in powder form in a proportion of 50  
parts tyrosine and 3 parts histidine. This product is then portioned into  
gelatin capsules so that each contains 500 mg. of tyrosine 30 mg.  
10       histidine and the capsules are administered as in Example 8.

### Example 13

15       A formulation as in Example 12 that contains cocoa in addition to  
tyrosine and histidine may prepared by blending in powder form 50  
parts of cocoa with 50 parts tyrosine and 3 parts histidine. Gelatin  
capsules are filled with the powder blend so that each gelatin capsule  
contain 500 mg. of tyrosine 30 mg. histidine and 500 mg. of cocoa. This  
20       formulation is administered as in example 8.

### Example 14

25       A formulation of histidine with tryptophan in the form of  
enzyme hydrolyzed protein may be prepared as follows. Enzyme  
hydrolyzed milk protein (casein) in dry powder form containing  
approximately 18 mg. tryptophan per gram is blended with histidine in  
powder form in a proportion of 200 parts hydrolyzed protein and 3 parts  
histidine. This product is then portioned into gelatin capsules so that a  
30       single dose of 30 mg. histidine and 2 gm. of hydrolyzed milk protein,  
which provides approximately 32 mg. of tryptophan, is contained in  
three capsules. The capsules are administered as in Example 8.

35

### Example 15

A formulation as in Example 14 that contains cocoa in addition to hydrolyzed milk protein and histidine may be prepared by blending in powder form 50 parts of cocoa with 200 parts of the hydrolyzed milk protein and 3 parts histidine. Gelatin capsules are filled with the powder blend so that three capsules together contain a single dose of 30 mg. histidine, 2 gm. of hydrolyzed milk protein, which provides approximately 32 mg. of tryptophan, and 500 mg. of cocoa. This formulation is administered as in example 8.

10

Following examples 16 through 18 illustrate the practice of the invention utilizing unhydrolyzed protein, together with a proteolytic enzyme, as the source of the neurotransmitter precursor tryptophan, both with and without concomitant application of a xanthine and/or histidine as an additional neurotransmitter precursor.

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### Example 16

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This example illustrates the administration of tryptophan in accordance with this invention by giving to the subject orally unhydrolyzed protein together with a proteolytic enzyme which will hydrolyze the protein when it enters the gastrointestinal tract to release the tryptophan.

25

Specifically 10 grams of whey powder and approximately 40 mg. of papain powder were administered to a subject orally, on an empty stomach. With this high dosage, tryptophan was released in the G.I. tract in an amount to induce appetite suppression, without the administration of xanthine. However, the subject experienced very pronounced grogginess that lasted for several hours.

30

Later, to the same subject, between 1 and 2 grams of whey powder, approximately 40 mg. of papain powder and 40 mg. of cocoa were administered, on an empty stomach. This formulation induced appetite suppression in the subject and no grogginess was experienced.

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This procedure provides an easy mode of administering tryptophan using natural food sources together with xanthine to produce appetite suppression without undue grogginess.

Adminstration of this tryptophan source without xanthine, or a synergistic neurotransmitter precursor, required such a high dosage level to acheive appetite suppression that the side effects (grogginess) were unacceptable.

5

### Example 17

10 A formulation of cocoa with tryptophan in the form of unhydrolyzed protein together with a proteolytic enzyme to hydrolyze the protein in the G. I. tract may be prepared as follows. Whey in dry powder is blended with papain and cocoa in powder form in a proportion of 200 parts by weight of hydrolyzed protein, 4 parts papain and 50 parts cocoa. This product is then portioned into gelatin capsules  
15 so that each contains 500 mg. cocoa and 2 gm. of whey and 40 mg. papain. Hydrolysis of the whey in the gastrointestinal tract provides a dose of approximately 50 mg. of tryptophan. The capsules are administered as in Example 8.

20

### Example 18

A formulation is prepared and administered as in Example 17 but with the addition thereto of 3 parts histidine, thus additionally  
25 providing 30 mg. of histidine per capsule dosage.

As can be seen from the foregoing, the synergistic combinations of the invention allow reduced doses of the individual components to  
30 be used to achieve the desired effects and particularly of the neurotransmitter precursors. The reduced doses decrease the side effects caused by the large doses heretofore necessary to achieve the desired effects. Our invention allows appetite suppression and reduction of carbohydrate craving to be achieved at doses levels which  
35 are considered safe by regulatory authorities. Previous attempts to use certain of the components in isolation were either ineffective or required dosages which caused side effects.



5 The decreased dose of tryptophan, for example, allows reduction of carbohydrate craving without causing feelings of grogginess or safety concerns associated with higher doses. The reduced dose of tyrosine allows appetite suppression without the agitation and anxiety induced by amphetamines. The reduced dose of histidine reduces or eliminates potential side effects of histamine.

It is further seen that the combinations of the invention enable the use of naturally occurring substances thereby enhancing their regulatory approval and market acceptance.

10 Although the description above contains many specificities, these should not be construed as limiting the scope of the invention but as merely providing illustrations of some of the presently preferred embodiments of this invention. Various other embodiments and ramifications are possible within it's scope.

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## Claims

1. A method for suppressing appetite in an animal subject which comprises concomitantly administering to the subject tryptophan in an amount effective to enhance synthesis of serotonin in the brain, in a dose of less than 100 mg, and a xanthine in an amount effective to enhance neural release of serotonin in the brain.
2. A method as in claim 1 and wherein the xanthine comprises caffeine.
3. A method as in claim 2 and wherein the caffeine administered is in a dose of between 1 and 200 mg.
4. A method as in claim 1 and wherein the xanthine comprises theobromine.
5. A method as in claim 4 and wherein the theobromine administered is in a dose of between 1 and 2,000 mg.
6. A method as in claim 1 and wherein the xanthine is in the form of cocoa.
7. A method as in claim 6 and wherein the cocoa administered is in a dose of between 1 and 2,000 mg.
8. A method as in claim 1 and wherein the tryptophan is administered in the form of enzyme hydrolyzed protein.
9. A method as in claim 8 and including the concomitant administration to the subject of a carbohydrate in an amount per dose sufficient to stimulate insulin production in the subject.
10. A method for suppressing appetite in an animal subject which comprises concomitantly administering to the subject a dopamine and norepinephrine precursor selected from phenylalanine and tyrosine in an amount effective to enhance synthesis of dopamine and norepinephrine in the brain, and a xanthine in an amount effective to increase neural release of dopamine and epinephrine in the brain.
11. A method as in claim 10 and including the administration of tryptophan to the subject in accordance with claim 1 at an interval of at

between 20 minutes and 24 hours from the time of administration of the dopamine and norepinephrine precursor.

12. A method as in claim 10 and wherein the dopamine and norepinephrine precursor administered is in a dose of between 10 and 700 mg.

13. A method as in claim 12 and wherein the dopamine and norepinephrine precursor administered is in a dose of less than 600 mg.

14. A method as in claim 10 and wherein the xanthine comprises caffeine.

15. A method as in claim 14 and wherein the caffeine administered is in a dose of between 1 and 200 mg.

16. A method as in claim 10 and wherein the xanthine comprises theobromine.

17. A method as in claim 16 and wherein the theobromine administered is in a dose of between 1 and 2,000 mg.

18. A method as in claim 10 and wherein the xanthine is in the form of cocoa.

19. A method as in claim 18 and wherein the cocoa administered is in a dose of between 1 mg. and 20 grams.

20. A method for suppressing appetite in an animal subject which comprises concomitantly administering to the subject histidine in an amount effective to enhance synthesis of histamine in the brain and a xanthine in an amount effective to increase neural release of histamine in the brain.

21. A method as in claim 20 and wherein the histidine dose administered is between 1 and 500 mg.

22. A method as in claim 20 and wherein the xanthine comprises caffeine.

23. A method as in claim 22 and wherein the caffeine administered is in a dose of between 1 and 200 mg.

24. A method as in claim 20 and wherein the xanthine comprises theobromine.

25. A method as in claim 24 and wherein the theobromine administered is in a dose of between 1 and 2,000 mg.
26. A method as in claim 20 and wherein the xanthine is in the form of cocoa.
27. A method as in claim 26 and wherein the cocoa administered is in a dose of between 1 mg. and 20 grams.
28. A method for suppressing appetite in an animal subject which comprises concomitantly administering to the subject the histamine precursor histidine in an amount effective to enhance synthesis of histamine in the brain and a second neurotransmitter precursor selected from tryptophan, phenylalanine and tyrosine in an amount effective to enhance synthesis in the brain of the neurotransmitters synthesized from the second precursor.
29. A method as in claim 28 and wherein the histidine dose administered is between 1 and 500 mg.
30. A method as in claim 28 and wherein the second precursor administered comprises tyrosine in a dose of between 1 and 600 mg.
31. A method as in claim 28 and wherein the second precursor administered comprises tryptophan in a dose of between 1 and 100 mg.
32. A method as in claim 28 and wherein the second precursor is tryptophan and the tryptophan is administered in the form of enzyme hydrolyzed protein.
33. A method as in claim 32 and including the concomitant administration to the subject of a carbohydrate in an amount per dose sufficient to stimulate insulin production in the subject.
34. A method as in claim 28 and including the concomitant administration to the subject of a xanthine in an amount effective to increase neural release in the brain of histamine and of the neurotransmitters synthesized from the second precursor.
35. A method as in claim 34 and wherein the xanthine comprises caffeine administered is in a dose of between 1 and 200 mg.

36. A method as in claim 34 and wherein the xanthine comprises theobromine administered is in a dose of between 1 and 2,000 mg.
37. A method as in claim 34 and wherein the xanthine is in the form of cocoa administered is in a dose of between 1 mg. and 20 grams.
38. A method for suppressing appetite in an animal subject which comprises concomitantly administering to the subject protein in an amount to comprise, upon enzyme hydrolysis thereof, sufficient tryptophan effective to enhance synthesis of serotonin in the brain, a proteolytic enzyme in an amount to hydrolyze the protein in the gastrointestinal tract to liberate the tryptophan and a xanthine in an amount effective to enhance neural release of serotonin in the brain.
39. A method as in claim 38 and wherein the xanthine comprises theobromine administered is in a dose of between 1 and 2,000 mg.
40. A method as in claim 38 and wherein the xanthine is in the form of cocoa.
41. A method for suppressing appetite in an animal subject which comprises concomitantly administering to the subject protein in an amount to comprise, upon enzyme hydrolysis thereof, sufficient tryptophan effective to enhance synthesis of serotonin in the brain, a proteolytic enzyme in an amount to hydrolyze the protein in the gastrointestinal tract to liberate the tryptophan and the histamine precursor histidine in an amount effective to enhance synthesis of histamine in the brain.
42. A method as in claim 41 and including the concomitant administration to the subject of a xanthine in an amount effective to increase neural release in the brain of histamine and of serotonin.
43. A composition for suppressing appetite in an animal subject, in unit dosage form, comprising tryptophan, in an amount between 1 mg and 100 mg per dose, and a xanthine in an amount effective to enhance neural release of serotonin in the brain of the subject.
44. A composition as in claim 43 and wherein the xanthine comprises theobromine in an amount of between 1 and 2,000 mg. per dose.

44. A composition as in claim 43 and wherein the xanthine comprises theobromine in an amount of between 1 and 2,000 mg. per dose.
45. A composition as in claim 43 and wherein the xanthine comprises caffeine in an amount of between 1 and 200 mg. per dose.
46. A composition as in claim 43 and wherein the xanthine is in the form of cocoa.
47. A composition as in claim 43 and wherein the tryptophan is present in the composition in the form of enzyme hydrolyzed protein.
48. A composition as in claim 47 and wherein the composition further comprises a carbohydrate, in an amount per dose sufficient to stimulate insulin production in a subject.
49. A composition for suppressing appetite in animal subject, in unit dosage form, comprising a dopamine and norepinephrine precursor, in an amount in an amount effective to enhance synthesis of dopamine and norepinephrine in the brain, and a xanthine in an amount effective to increase neural release of dopamine and epinephrine in the brain.
50. A composition as in claim 49 and wherein the xanthine comprises theobromine in an amount of between 1 and 2,000 mg. per dose.
51. A composition as in claim 49 and wherein the xanthine comprises caffeine in an amount of between 1 and 200 mg. per dose.
52. A composition as in claim 49 and wherein the xanthine is in the form of cocoa in the amount of between 1 and 2,000 mg. per dose.
53. A composition as in claim 49 and wherein the precursor is tyrosine in an amount per dose is between 1 and 600 mg.
54. A composition as in claim 53 and wherein the amount of tyrosine per dose is less than 500 mg.
55. A composition for suppressing appetite in animal subject, in unit dosage form, comprising histidine, in an amount in an amount effective to enhance synthesis of histamine in the brain, and a xanthine in an amount effective to increase neural release of histamine in the brain.

56. A composition as in claim 55 and wherein the xanthine comprises theobromine in an amount of between 1 and 2,000 mg. per dose.
57. A composition as in claim 55 and wherein the xanthine comprises caffeine in an amount of between 1 and 200 mg. per dose.
58. A composition as in claim 55 and wherein the xanthine is in the form of cocoa in the amount of between 1 mg. and 20 grams per dose.
59. A composition as in claim 55 and wherein the amount of histidine per dose is between 1 and 600 mg.
60. A composition for suppressing appetite in animal subject, in unit dosage form, comprising the histamine precursor histidine in an amount effective to enhance synthesis of histamine in the brain and a second neurotransmitter precursor selected from tryptophan, phenylalanine and tyrosine in an amount effective to enhance synthesis in the brain of the neurotransmitters synthesized from the second precursor.
61. A composition as in claim 60 and wherein the amount of histidine per dose is between 1 and 600 mg
62. A composition as in claim 60 and wherein the second precursor administered comprises tyrosine in a dose of between 1 and 600 mg.
63. A composition as in claim 60 and wherein the second precursor administered comprises tryptophan in a dose of between 1 and 100 mg.
64. A composition as in claim 60 and wherein the second precursor is tryptophan in the form of enzyme hydrolyzed protein.
65. A composition as in claim 64 and further including a carbohydrate in an amount per dose sufficient to stimulate insulin production in the subject.
66. A composition as in claim 60 and wherein the composition further comprises a xanthine in an amount effective to increase neural release in the brain of histamine and of the neurotransmitters synthesized from the second precursor.
67. A composition as in claim 66 and wherein the xanthine comprises theobromine in an amount of between 1 and 2,000 mg. per dose.

69. A composition for suppressing appetite in animal subject, in a dry unit dosage form, comprising powdered protein in an amount to comprise, upon enzyme hydrolysis thereof, sufficient tryptophan effective to enhance synthesis of serotonin in the brain and a proteolytic enzyme in an amount to hydrolyze the protein in the gastrointestinal tract to liberate the tryptophan and a xanthine in an amount effective to enhance neural release of serotonin in the brain.
70. A composition as in claim 69 and wherein the protein is in the amount of between about one half gram to 30 grams per unit dose and the enzyme is in the amount of between 30 and to 50 mg. per gram of protein.
71. A composition as in claim 70 and wherein the enzyme is papain.
72. A composition for suppressing appetite in animal subject, in a dry unit dosage form, comprising powdered protein in an amount to comprise, upon enzyme hydrolysis thereof, sufficient tryptophan effective to enhance synthesis of serotonin in the brain, a proteolytic enzyme in an amount to hydrolyze the protein in the gastrointestinal tract to liberate the tryptophan and the histamine precursor histidine in an amount effective to enhance synthesis of histamine in the brain.
73. A composition as in claim 72 and further comprising a xanthine in an amount effective to increase neural release in the brain of histamine and of serotonin.



## INTERNATIONAL SEARCH REPORT

International application No.

T/US97/12408

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/52, 31/195, 35/12, 38/43

US CL : 514/263, 561; 424/520, 94.1

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/263, 561; 424/520, 94.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2,004,183 A (THE PHARMACEUTICAL EXPORT PROMOTION COUNCIL) 28 March 1979, see the entire document.	1-73
Y	US 4,897,380 A (POLLACK et al) 30 January 1990, see the entire document.	1-73
Y	WO 91/10441 A1 (MEDGENIX GROUP S.A.) 25 July 1991, see the entire document.	1-73
Y	US 3,867,539 A (HENKIN) 18 February 1975, see the entire document.	1-73
Y	US 5,019,594 A (WURTMAN et al.) 28 May 1991, see the entire document.	1-73

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 SEPTEMBER 1997	Date of mailing of the international search report 08 OCT 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEAN C. WITZ Telephone No. (703) 308-0196

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/12408

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,210,637 A (WURTMAN et al.) 01 July 1980, see the entire document.	1-73

Form PCT/ISA/210 (continuation of second sheet)(July 1992)\*

# INTERNATIONAL SEARCH REPORT

International application No.

T/US97/12408

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CA, APS, MEDLINE BIOSIS, WPIDS:

search terms: (suppress? or reduc? or decreas?(5a)appetit?) and (tryptophan or histidine or tyrosine or phenylalanine or caffeine or xanthine)

Form PCT/ISA/210 (extra sheet)(July 1992)\*

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